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MARGARINES AND CORONARY ARTERY DISEASE

The Food and Drug Administration has banned references to blood cholesterol and heart disease in the labeling of products containing polyunsaturated fatty acids; but this ban has not discouraged the introduction of new margarines containing oils with a high concentration of unsaturated fatty acids, and their promotion, directly or indirectly, as dietary aids in combating heart disease.

The question for the physician is whether he should advise patients, especially those with a personal or family history of atherosclerosis, to use one of the new products. To start with, there is no evidence that simply substituting one of the new margarines for ordinary margarine or for butter, in an otherwise unchanged diet, will lower blood lipids or favorably influence the course of any vascular disease. It is true that a diet in which about three quarters of all the fat consumed is polyunsaturated will reduce serum cholesterol; but it has not been established that such reduction will have any effect on the incidence or severity of atherosclerosis or coronary disease.

TRIGLYCERIDES - Some investigators, including M. J. Albrink, et al. (Am. J. Med., 31:4, 1961), believe that serum triglyceride (neutral fat) levels have a more meaningful association with coronary disease, especially after age 50. But a diet high in unsaturated fats or oils and low in animal fats will have little if any effect on triglycerides, even though it will lower cholesterol levels appreciably. On the other hand, triglycerides can be lowered by increasing the fat content of the diet, even with some saturated fats, provided there is a calorically equivalent reduction in carbohydrates. The substitution of unsaturated vegetable-oil calories for carbohydrate calories appears to be the best means of lowering the levels of both cholesterol and triglycerides (E. H. Ahrens, Jr., et al., Transactions, Assoc. Am. Phys., 1961, to be published).

In the absence of acceptable evidence that reduction of either cholesterol or triglyceride levels by diet (or drugs or hormones) can alter the incidence or progress of vascular disease, any dietary measures the physician prescribes must be considered experimental. Fortunately, aside from gastrointestinal discomfort in some patients, there appears to be no harm in the substitution of unsaturated vegetable fats for animal fats or for carbohydrates; and if the physician feels that a patient will take comfort from some positive dietary measure, he can safely follow the advice of the American Heart Association that men and

women who have had heart attacks or strokes and men who seem to be heading for such attacks should substitute polyunsaturated fats for a substantial part of saturated fats. In such a diet, the new margarines can provide some of the calories more palatably than liquid oils.

CHOICE OF BRAND - There is at present no basis for a choice among the various margarines apart from taste preferences. The differences in saturation among the margarines are not necessarily significant; factors other than unsaturation may also enter into cholesterol-lowering effects, for example, the molecular size of the fatty acids, and the geometric configuration of the double bonds in the unsaturated fats (S. A. Hashim, et al., Lancet, 1:1105, 1960).

Studies which will take five to ten years to complete may show that certain diet alterations do reduce the incidence or progress of vascular disease. Until such time the simplest prophylactic measures are probably year-around moderate exercise and, for overweight patients, reduction of total caloric intake.

FLEXIN

Zoxazolamine (Flexin — McNeil), offered as a skeletal muscle relaxant and more recently as a uricosuric agent, has been withdrawn from the market by the manufacturer "because of reports in medical literature, and observations...by physicians, which suggest that Flexin may be associated with the development of hepatitis in an occasional patient."

At least four fatal cases of hepatic injury attributed to the use of Flexin have been reported (Editorial, N. E. J. Med., 260:1296, 1959; H. J. Carr, Jr. and Q. F. Knauer, N. E. J. Med., 264:977, 1961), and many more non-fatal cases of hepatitis have been observed. Reversible renal damage has also appeared in patients on the drug, probably as the result of transient uric acid crystalluria.

BENEMID - Commenting on the use of Flexin in patients with chronic gout, The Medical Letter (3:11, Feb. 3, 1961) said that probenecid (Benemid — Merck) should be considered the uricosuric agent of first choice until more experience had established the safety of Flexin. Benemid is not entirely without side effects. It causes urticaria in about five per cent of patients, and gastrointestinal symptoms in about eight per cent (J. E. Seegmiller, Med. Clin. N. Amer., 45:1259, Sept. 1961). One case of a probenecid-induced nephrotic syndrome has been reported (T. F. Ferris, et al., N. E. J. Med., 265:381, Aug. 24, 1961), but it was completely reversible, and in the ten years of its use Benemid has had an excellent record of freedom from serious toxicity.

Sulfinpyrazone (Anturane — Geigy) is another effective uricosuric drug; although serious toxic or sensitivity reactions have not yet been reported, Anturane is chemically related to phenylbutazone and it is too soon to be sure that the drug will not produce some of the latter's serious toxicity, particularly with long use.

As for the muscle-relaxing effects of Flexin, the withdrawal of the drug will not deprive physicians of a potent therapeutic agent. The reported clinical

trials on which the muscle-relaxing claims were based were, with few exceptions, uncontrolled. One well-controlled study (E. Denhoff and R. H. Holden, N. E. J. Med., 264:475, 1961) showed Flexin to be no more effective than a placebo in influencing neuromotor function. M. Watkins and M. H. Hale (JAMA, 165:830, 1957) found that Flexin had "no appreciable effect" in a controlled study with 95 spastic or athetoid children.

THE TETRACYCLINE ANTIBIOTICS

The broad-spectrum glamour of the tetracycline antibiotics has been somewhat tarnished by the occurrence of serious superinfections following their use, and by the increasing incidence of resistant organisms. Nevertheless, they are still effective in some bacterial, rickettsial and viral infections; and they are the drugs of first choice in the prophylaxis and treatment of severe chronic bronchitis or bronchiectasis.

In the treatment of Hemophilus influenzae meningitis, either a tetracycline or chloramphenicol should be tried first, alone or in combination with a sulfonamide or streptomycin. The tetracyclines are also highly effective in acute Hemophilus influenzae laryngitis, and in some cases of primary atypical pneumonia, such as Eaton-agent pneumonia. For other infections severe enough to require antibiotic therapy, the use of a tetracycline offers no clear-cut advantage unless in vitro tests show that the infecting organisms are especially susceptible to it, or the patient's history suggests intolerance to other drugs. The early hope that the broad-spectrum properties of the tetracyclines would make it unnecessary to determine the bacterial cause of an infection has vanished.

IMPROPER USES - The most serious abuse of the tetracyclines occurs in their employment for prophylaxis against bacterial complications of acute viral respiratory diseases and to prevent pneumonia and other postoperative infections. Recent studies have shown little justification for such use of any antibacterial agent. The emergence of many resistant enteric organisms has greatly reduced the effectiveness of the tetracyclines in the preoperative preparation of the bowel. Of even greater concern has been the mounting resistance of Staphylococcus aureus to the tetracyclines; resistant staphylococci repeatedly have been found with greater frequency in tetracycline-treated patients than in patients treated with limited-spectrum antibiotics such as erythromycin.

In early studies the tetracyclines were almost as effective as penicillin against acute streptococcal respiratory infections, but a decreased susceptibility of group A streptococci has recently been observed. Such observations can only reinforce the caution against the routine use of tetracyclines in the treatment of common acute respiratory infections. Because of their lack of bactericidal properties, even with sensitive microorganisms, the tetracyclines are relatively ineffective when they are used alone in the treatment of infections such as bacterial endocarditis which have little tendency towards spontaneous cure.

Four analogues of the antibiotic are available: tetracycline (various manufacturers), chlortetracycline (Aureomycin — Lederle), oxytetracycline (Terra-

mycin — Pfizer), and demethylchlortetracycline (Declomycin — Lederle). (A 150-mg. dose of Declomycin is equivalent to a 250-mg. dose of the other tetracyclines.) Tetracycline is offered either as the plain hydrochloride or in buffered form with phosphate complexes (various manufacturers), citric acid (Achromycin V — Lederle) or glucosamine (Tetracyn — Pfizer). Despite the claim that buffering results in improved absorbability from the gastrointestinal tract, plain tetracycline hydrochloride is probably equally well absorbed (I. O'Reilly and E. Nelson, J. Pharm. Sci., 50:413, 1961). The evidence also indicates that the differences in antibacterial effectiveness among the different analogues are too small to permit a meaningful choice on the basis of in vitro tests.

GASTROINTESTINAL TOXICITY - Neither is there a very clear basis for a choice with respect to gastrointestinal toxicity. In general, such toxicity is proportional to dose and is a serious limiting factor with many patients. If a significant difference does exist, tetracycline hydrochloride and demethylchlortetracycline are probably the analogues with the most favorable ratio of therapeutic action to gastrointestinal toxicity. Exaggerated sunburn (phototoxicity) frequently occurs with demethylchlortetracycline, and if it is given to ambulatory patients they should be warned of this effect.

Despite the introduction of N-(pyrrolidinomethyl)tetracycline (Syntetrin — Bristol), which is claimed to give increased serum concentrations with tolerated intramuscular doses, the limitation on maximum dose and the need for frequent injections still make intramuscular administration undesirable. Slow intravenous infusions can, however, give high serum concentrations. Thrombophlebitis is a frequent complication of intravenous administration.

With most organisms sensitive to the tetracyclines, an adult dosage of 1 Gm. a day (600 mg. for Declomycin) is likely to be effective. Larger doses are usually given to more severely ill patients. Where absorption may be delayed, a large initial loading dose should be given or intravenous administration should be employed until a response has been observed. When one tetracycline is ineffective, changing to another will almost never benefit the patient. The change should be to a different antibiotic, with the choice determined by laboratory studies.

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Sworn to and subscribed before me this 27th day of September, 1961, Max Kalichstein, Notary Public, State of New York

Arthur Kallet, Managing Director

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